Bioimpedance Method on Lymphedema Diagnosis

A Thesis

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By

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ABSTRACT

Lymphedema, a common complication due to breast cancer treatment, is presented as swelling of a limb. This project studies the electrical property of the limb tissue of breast cancer survivors in order to help diagnose lymphedema. Electrical impedance under a range of frequencies is measured. An electrical equivalent circuit is simulated to model the swelling tissue. The impedance data are analyzed using Matlab to calculate electrical parameters of the modeling circuits. Confirmed lymphedema patients are compared to normal volunteers to identify electrical parameters that may be correlated with development of lymphedema. Change of the correlated electrical parameters of patients in the simulated model helps to provide physiological information on lymphedema which is important in clinical treatment. The bioimpedance Wessel curves of long term lymphedema patients seem to deviate from Cole model. More complicated models that have more nonlinearity with frequency are required to further explain the deviation.

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This is dedicated to the everyone who helped me with the first thesis in my life.

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CHAPTER 1

INTRODUCTION

1.1 Motivation

Cancer is one of the most threatening diseases in human society. It is estimated that in 2010, there were 739,940 women who died of cancer, among which 207,090 women had breast cancer. In 2003-2007, the median age of death due to breast cancer was 68; 20.8% died between 55 and 64; 19.7% between 65 and 74; and 22.6% between 75 and 84 [1]. The largest fears for cancer survivers are reaccurance and complications. Treatments of cancer include chemotherapy, radiation therapy, surgery and drugs. A lot of patients have to go through multiple types and courses of therapies which induce fatigue, hair loss, pain and other disorders.

Lymphedema is one of the common post operation complications of breast cancer. American Cancer Society conducted a survey which showed that among the approximately 2 million breast cancer survivors in US, 20% developed lymphedema [8]. Lymphedema presents as swelling due to blockage of lymph passages in the lymphatic system. There are two types of lymphedema: primary and secondary. Primary lymphdema is caused by a genetic disorder while secondary lymphedema is usually caused by surgery or trama.

Currently, there is no effective method to diagnose or to prevent lymphedema. The reason lies in the fact that the detailed mechanisms of the disease are not clear. Most cancer patients have their affected lymph nodes removed in the surgery but doctors are not sure why only about 20% patients develop lymphedema. Clinically, lymphedema is diagnosed by measuring volume and diameter of the limbs [9]. Physicians use a device called perometer to measure the swelling of limbs. A perometer is a 3-D LED scanning system. It uses several infrared light emitters to shoot light beams from different angles at the limb and then it detects reflections of light to cast images of cross sections of the limb. Measuring at various positions along the limb can tell doctors the severity of swelling [9].

Lymphedema can be temporary, but many times it is a chronic disease [5]. Diagnosis based on external geometry of limbs can not provide enough information on the development or physiological causes of the disease. Therefore, no effective treatments can be prescribed. Most doctors advise patients to have a healthy diet and some massage to relieve the swelling. When lymphedema progresses to its later fibrosis stage, swelling tissues get hardened and stiff. Unfortunately for the patient, at this fibrosis stage, nothing can relieve the condition, and the swelling becomes permanent [4].

1.2 Problem Statement

A perometer can measure the volume of the limb to indicate the stages of swelling but this does not reflect the underlying physiological problem. MRI can form good quality images of the soft tissue but doing MRI on a regular basis is quite expansive. Once the patient reaches the fibrotic stage, the disease becomes untreatable. So

close monitoring of the condition of the patients and preventing lymphedema from progressing to later stages are crucial to the patients.

Bioimpedance as a method is relatively cheap and fast compared to MRI and reveals more underlying physiology of the swelling than measuring volume of the limb. Bioimpedance measurement can be easily performed repeatedly even over a short period of time. The bioimpedance method can detect minute changes in limb tissue and therefore, it can estimate the potential risk for the patient to develop lymphedema. Early detection and prediction can guide physicians to apply appropriate treatments before swelling becomes permenent. In this way, we may be able to prevent long term lymphedema and improve breast cancer survivors life qualities.

This project develops electrical equivalent models to simulate body tissue and identify electrical parameters that are correlated to lymphedema. Based on bioimpedance characteristics of lymphedema tissue, analysis of patients' tissue bioimpedance information can help diagnose and predict lymphedema.

1.3 Organization

This thesis discusses the lymphedema disease, Cole model and Levenberg-Marquardt Algorithm used in this project first, and then explains the analysis process of bioimpedance data and finally gives results, conclusions and discussion of future work.

CHAPTER 2

LYMPHEDEMA

2.1 Bioimpedance Method Characterizes Lymphedema

The bioimpedance method measures the complex impedance of tissue as a function of frequency. For each value of frequency, a real and an imaginary part of the impedance are calculated. The matrix of complex impedance reflects the electrical property of the tissue. Conductive and reactive properties of the tissue reflect the amount of lymph liquid that is aggregated and the permeability of the cell membranes.

Treatments of breast cancer destroy cancer cells, but they also inevitably damage benign tissue. The lymphatic system consists of lymph nodes and lymph vessels that carry lymph liquids throughout the body. In the lymph vessels, excess body fluids flow back to blood circulation system. Lymph nodes host white blood cells in lymph liquids to fight infections and injuries. Surgery or therapies damage the lymphatic system causing obstruction in lymph vessels. When blockage happens, intra- lymphatic pressure increases and lymph vessels dilate. Lymph liquid aggregates in the tissue around the site of the blockage causing swelling. Some scholars and researchers believe the excess lymph liquid create a ẗhird space ïn the tissue. It is still not clear how the excess body liquid gathers in the intercellular space. Lymph

liquid has high protein content that could gradually cause fibrosis in tissue and cell membranes [3].

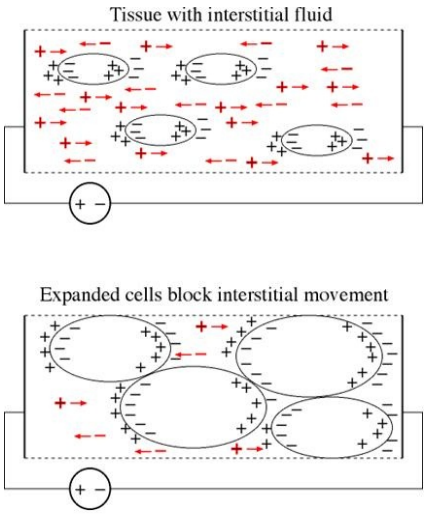


Figure 2.1: Bioimpedance method on tissue.

Human tissue can be simulated as leaky capacitor and resistor combinations. Semipermeable membranes can actively and passively allow some ions and small molecules to pass through while leaving the rest of the ions and large protein molecules outside the cell. Under external voltage excitations, charged ions move to opposite directions. Some ions are partially blocked by the cell membranes (capacitive); others can pass through the membranes or move relatively freely in interstitial space (resistive) as shown in Fig. 2.1. Thus, cells themselves act as capacitors since they separate charges and interstitial fluids behave as resistors. The electrical behavior of the tissue can therefore tell the stories of swelling of cells and permeabilities of the cell membranes.

Frequency	Impedance Real Part	Impedance Imaginary Part
3.0842	319.2945	10.2801
3.1471	319.3528	10.6795
3.2101	319.1783	10.6043
⋮	⋮	⋮

Table 2.1: Bioimpedance data

In the case of lymphedema shown in the bottom image in Fig. 2.1, cells expand and block more ions. Fewer ions can move freely around the cells. When limb tissue becomes fibrotic, cell membranes lose the ability of selectively passing through molecules and substances, which greatly alters the corresponding resistive and capacitive properties of the tissue. The bioimpedance method takes advantage of the changes in electrical parameters to study the progression of lymphedema.

2.2 Experimental Device

The project uses a bioimpedance machine manufactured by L-DEX. The L-DEX machine sends a sinusoidal voltage signal from its signal electrode and detects the current signal from its detection electrode. The signal electrode is attached to the patient's wrist and the detector at ankle of the same side. L-DEX machines generate sinusoids that sweep through a range of frequencies. At each frequency, the machine abstracts the magnitude and phase of the detected current and then calculates the impedance of the tissue. The output impedances from the L-Dex machine are shown in Table 2.1. Bioimpedance measurement generates a series of complex impedances as a function of the frequency sequence.

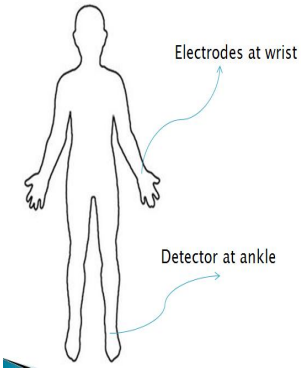


Figure 2.2: Bioimpedance measurement set up.

2.3 Bioimpedance Measurement

The L-Dex machine detects the magnitude and phase of the received current signal in reference to the transmitted sinusoids. The ratio of the transmitted voltage signal and the received current is the impedance of the tissue. Then, L-Dex machine turns the magnitude and phase of the impedance to real and imaginary part of the complex impedance.

$$V(t) = cos(2 * \pi f_0 t); \tag{2.1}$$

$$I(t) = Acos(2 * \pi f_0 t + \theta); \tag{2.2}$$

$$Z = \frac{V}{I} = A\angle\theta = Real + jImag \tag{2.3}$$

where V(t) = transmitted voltage signal, I (t) = detected current signal, and Z is the bioimpedance of the tissue.

Previous studies have tried different places where the electrodes are connected to the patients in order to increase repeatability of the experiments [10]. The positions

of attachment are only specified as wrist and ankle which are not detailed enough to be perfectly repeatable. Even if the same technician performs the measurements every time, electrodes can still be connected at slightly different places each time, which can cause errors. Study shows that ankle and wrist have the smallest error relative to some other parts of the body [2].

The impedance data from the measurement is in fact the impedance of the entire tissue between the two electrodes which encompasses arm, body and leg. Variation in impedance data can be attributed to any changes in body and legs instead of arms. Comparison between measurement of the left and right arms of the same subject is necessary to exclude the irrelevant impact from other parts of the body. Impedance at low frequency reflects the resistive property of the tissue which are related to the size of the cells and permeability of the membranes. On the other hand, impedance at high frequency signifies the reactive part which corresponds to the impermeability and the obstruction of the ion flow.

2.4 Data Export

L-Dex measures the impedance of the tissue and stores the data in its built in memory. The software that comes with L-Dex machine can download some data to a PC. However, since the L-Dex package was not designed for further redevelopment and research, the software could not export the impedance vs. frequency measurement data. Impedance results are coded in a form specifically for the software to read, so the software can only display the raw data numbers. Data can not be copied, pasted or exported.

We started to gather data initially by manually capturing the data from the screen and typing into an Excel spreadsheet. But this process significantly limits the number of data points we are able to copy and also increases the probability of data error due to typos. The L-Dex machine sweeps 512 frequencies in every measurement which means it generates 512 complex numbers for each measurement. Every patient has left and right side measurements, thus each patient has 1024 complex numbers to be manually typed into spreadsheets. We decided to select 1 out of every 5 data points from the original data set in order to reduce labor work and also minimize human error. Typos can greatly compromise the quality and reliability of the data. However, the size of available data pool is reduced to a fifth of the measured data.

We later developed a solution to the data export problem which greatly improved the data acquisition process. When the software reads the data from the L-Dex machine, it saves a copy of the entire data information to the PC's RAM. Using an extra widget that searches a PC's RAM, we can then find the starting address of the data information. Provided that the data series is stored in consecutive memory addresses, a simple C program can be written to load the data at specific memory addresses from RAM. Manually searching RAM using the first data number in the series as a keyword is still necessary, but the entire 512 frequencies can be downloaded with no typing error.

This searching RAM approach was adopted for all analysis until the updated version of the software was released. Per our request, the new L-Dex software has additional export function that generates Excel spreadsheets that contain all measurement data.

CHAPTER 3

COLE MODEL

3.1 Overview

An electrical model describing the capacitive and resistive properties of the tissue at various frequencies is useful in further understanding the physical process behind lymphedema. The electrical model is the electrical equivalence of the tissue under measurement. It is a circuit that behaves similar to the tissue when observed from predefined terminals.

Electrical models are divided in descriptive and explanatory models. Descriptive models only reflect the electrical phenomena, in this case resembling the impedance characters of the tissue. The model as a whole when excited by certain frequencies, behaves like the tissue, but there is no correspondence between the smaller components of the model and subsystems in the tissue. The model does not necessarily exist as a biologic structure. Therefore, descriptive model can not satisfy our need of explaining physiological causes of lymphedema.

The other type is an explanatory model which compensates for the physiological process that the descriptive model is not able to represent. An explanatory model contains analogies to the physical mechanisms in biological tissue. It is believed

that the overall electrical properties of the tissue can be explained by properties of components that form the model [7]. According to the analogy between model and biological tissue, the dominant electrical properties of the tissue can thus be attributed to small subcomponents such as interstitial and intra-cellular fluids. Thus, bioimpedance data can provide information towards the physical status of the swelling of cells and increasing interstitial fluids which can be used to diagnose lymphedema. Electrical models may detect early swelling of cells before lymphedema symptoms begin to present in patients.

3.2 Equivalent Circuit with Ideal Components

Simple equivalent circuits contain only ideal elements which are normal resistors and capacitors. Ideal elements means that the circuit they form has an impedance or admittance that varies linearly with frequencies. For example, a capacitor has admittance that is proportional to exciting frequency:

$$Y_C = j\omega C \tag{3.1}$$

The simplest models are resistor in parallel with a capacitor or resistor in series with capacitor as shown in Fig. 3.1 and 3.3.

The impedance of the model as a function of frequency in parallel circuit case :

$$Z = R||\frac{1}{j\omega C} = \frac{\frac{R}{j\omega C}}{R + \frac{1}{j\omega C}} = \frac{R}{Rj\omega C + 1} \tag{3.2}$$

For a parallel R-C circuit, a Wessel diagram shown in Fig. 3.2, shows imaginary versus real part. The impedance represented in Wessel form is developed as:

$$Z = \frac{R}{Rj\omega C + 1} = \frac{R(R\omega Cj - 1)}{(R\omega C)^2 + 1} = \frac{R^2\omega C}{(R\omega C)^2 + 1}j - \frac{R}{(R\omega C)^2 + 1} \tag{3.3}$$

$$Real = -\frac{R}{(R\omega C)^2 + 1}; \tag{3.4}$$

$$Imag = \frac{R^2\omega C}{(R\omega C)^2 + 1}; \tag{3.5}$$

$$Imag^2 + (Real + R/2)^2 = R^2/4 \tag{3.6}$$

The impedance curve is a circle centered at (-R/2, 0) with a radius of R/2. In reality, a practical range of frequency is from Hz to MHz, which as shown in Fig. 3.2, is only a portion of circle.

In series circuit case:

$$Z = R + \frac{1}{j\omega C} \tag{3.7}$$

Here impedance is less interesting since the real part of impedance is independent of frequency and the Wessel plot shows only a straight line. Thus, for series circuit case, the reciprocal of impedance which is admittance of the circuit is studied.

$$Y = 1/Z = \frac{(wC)^2 R}{1 + (wCR)^2} + \frac{jCw}{R^2 + 1 + (wCR)^2} \tag{3.8}$$

$$Real = \frac{(wC)^2 R}{1 + (wCR)^2}; \tag{3.9}$$

$$Imaginary = \frac{jCw}{R^2 + 1 + (wCR)^2} \tag{3.10}$$

The admittance of the circuit is also a circle shape as shown in Fig. 3.4.

Parallel and series circuits are duals of each other, so they contain the similar information. They are just two forms of an electrical model.

In order to closer approximate human tissue which is a rather complicated biological system, more than two electrical elements are used to create the model. The possible equivalent circuits using two capacitors and one resistor or one resistor and two capacitors have impedance properties shown in Fig. 3.5

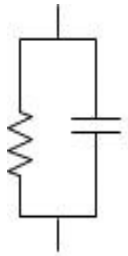


Figure 3.1: R and C parallel

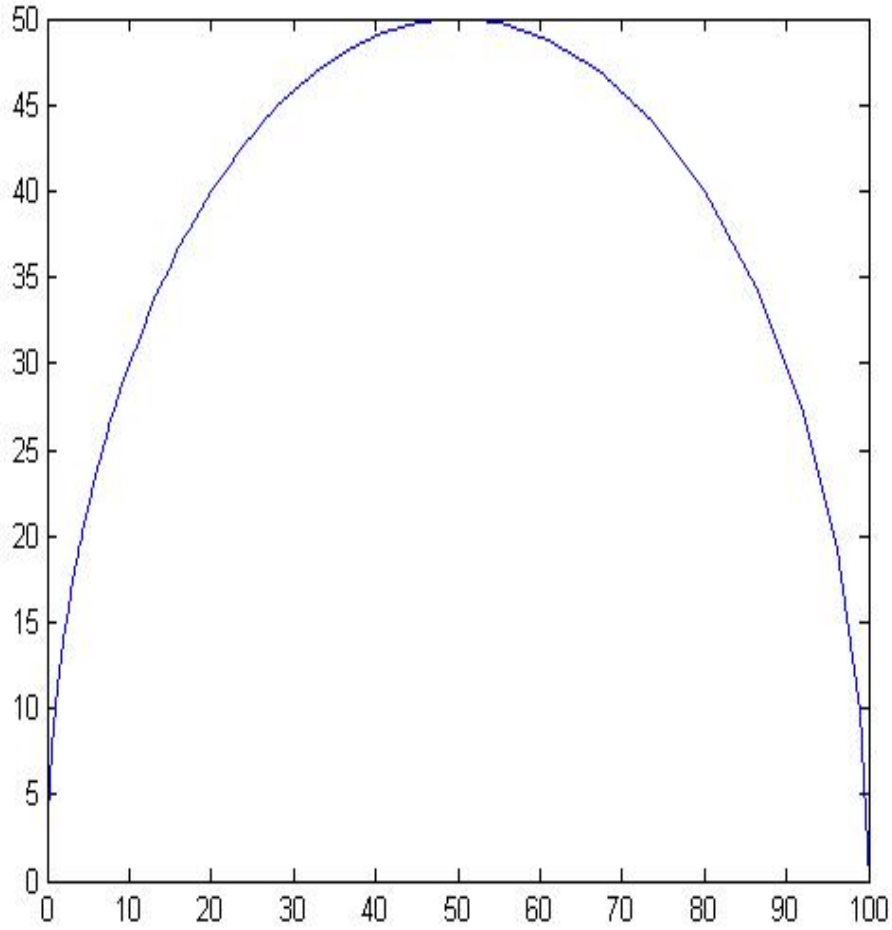


Figure 3.2: R and C parallel Wessel Diagram

Figure 3.3: R and C series

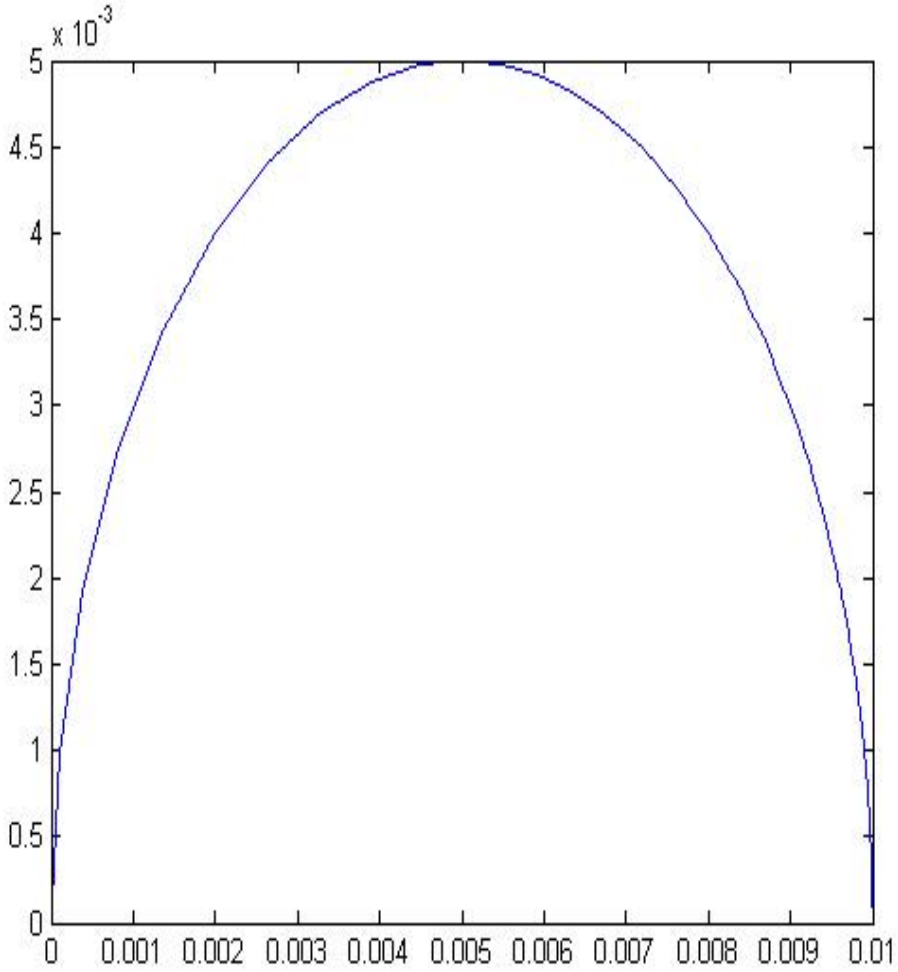


Figure 3.4: R and C series Wessel Diagram

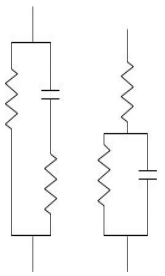


Figure 3.5: Equivalent circuit of three or more elements

3.3 Constant Phase Elements

Practically, biological tissue is likely to vary its electrical property with frequency. To add non-linearity to the equivalent model, a notion of constant phase elements (CPE) is introduced. The Cole model used in this project is based on CPEs. A CPE is an electrical element whose phase of complex impedance is independent of frequency. In other words, the impedance can have magnitude a function of frequency and phase constant.

$$Z_{CPE} = a + jb;$$

$$Phase = \arctan\left(\frac{b}{a}\right) = constant \tag{3.11}$$

Both imaginary and real parts need to be dependent on the same power of frequency in order to keep the phase constant.

$$real = a_0 w^{\alpha}, imaginary = b_0 w^{\alpha} \tag{3.12}$$

A time constant τ is defined as product of R and C in ideal linear case. For constant phase elements, τ is used as a scaling factor on frequency. The product of

ω and τ is unit-less. Thus, the real and imaginary parts can be expressed as

$$real = a_0 w\tau^{\alpha}; Imag = b_0 w\tau^{\alpha} \tag{3.13}$$

$$Z = R(jw\tau)^{-\alpha} = (cos(\alpha\pi/2) - jsin(\alpha\pi/2))w^{-\alpha}\tau^{-\alpha}R \tag{3.14}$$

Implementing the non-linear constant phase elements into circuits, the impedance becomes a function of frequency.

3.4 Cole Model

In 1940, Kenneth S. Cole published tissue impedance characteristic described as:

$$Z = Z_{\infty} + \frac{(R_0 - R_{\infty})}{(1 + (jw\tau)^{\alpha})} \tag{3.15}$$

He made some modification in later years to replace Z_{∞} with R_{∞} for clarity. [7] Finally, the Cole equation is often cited as :

$$Z = R_{\infty} + \frac{(R_0 - R_{\infty})}{(1 + (jw\tau)^{\alpha})} \tag{3.16}$$

The admittance version is written as $\frac{1}{Z}$ which is then decomposed into real and imaginary part:

$$Real = G_0 + \Delta G \frac{1 + (w\tau)^{-\alpha} cos(\alpha\pi/2)}{1 + 2(w\tau)^{-\alpha} cos(\alpha\pi/2) + (w\tau)^{-2\alpha}} \tag{3.17}$$

$$Imag = \Delta G \frac{(w\tau)^{-\alpha} sin(\alpha\pi/2)}{1 + 2(w\tau)^{-\alpha} cos(\alpha\pi/2) + (w\tau)^{-2\alpha}} \tag{3.18}$$

The Cole model circuit admittance form is represented in Fig. 3.6. CPE is represented using a resistor-like shape and a capacitor-like shape as shown in Fig. 3.6. The resistor part represents

$$Re(Z_{CPE}) = a_0 w^{\alpha}$$

and the capacitor represents

$$Imag(Z_{CPE}) = b_0 w^{\alpha}$$

The Wessel diagram of a Cole model is shown in Fig. 3.7. The locus of the Wessel diagram is elliptical with its center below real axis.

The parameter α as the exponent in the Cole model is believed to be a measurement of a distribution of relaxation time. The α parameter is not dependent on geometry of the measured tissue as long as the volume is constant [7]. The ideal models are special cases of generalized Cole model. When $\alpha = 0$, Cole model simplifies to idealized resistor; when α =1, Cole model simplifies to resistor and capacitor in series or in parallel.

Figure 3.6: Cole model admittance form

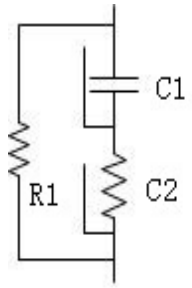
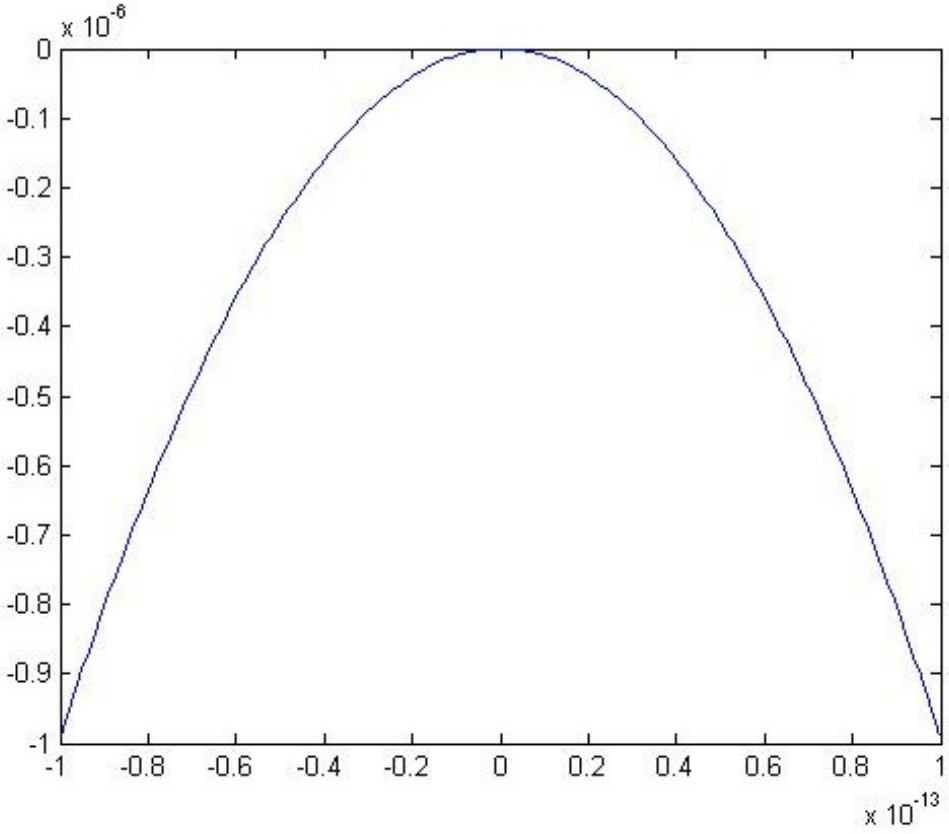


Figure 3.7: Cole model admittance Wessel diagram



CHAPTER 4

LM ALGORITHM

4.1 Overview

The Levenberg-Marquardt Algorithm (LMA) is an algorithm that optimizes a nonlinear function. LMA provides a numerical solution to the minimization problem on a generally nonlinear function over a space of parameters in the function. It is often used to do least square curve fitting which optimizes certain parameters to generate least square error fit of a given curve.

4.2 Algorithm

4.2.1 Problem Statement

Fit the data set:

$$\begin{array}{cccccc} X_{11} & X_{12} & X_{13} & ... & X_{1M} & Y_1 \\ X_{21} & X_{22} & X_{23} & ... & X_{2M} & Y_2 \\ X_{31} & X_{32} & X_{33} & ... & X_{3M} & Y_3 \\ ... & ... & ... & ... & ... & ... \\ X_{i1} & X_{i2} & X_{i3} & ... & X_{iM} & Y_i \\ ... & ... & ... & ... & ... & ... \\ X_{N1} & X_{N2} & X_{N3} & ... & X_{NM} & Y_N \end{array}$$

with a model:

$$y = f(x_1, x_2, x_3, ..., x_M; \beta_1, \beta_2, \beta_3, ..., \beta_K) = f(X; \beta)$$

The data are in a N by M+1 matrix that shows a function of M independent variables. The M-dimensional function takes N sets of values, of which each set corresponds to a Y. The model is a function of M variables with K parameters. The goal is to tune the K parameters in order to match the function value y to the data set.

The process is a iteration cycle. Starting with an initial guess, an error is calculated every time going through the iteration and is compared to the previous error. The error is defined as:

$$Error\Phi = \sum_{i=1}^{n} |Y_i - \hat{Y}|^2; \tag{4.1}$$

where $\hat{Y}$ is the predicted value based on previous iteration.

When f is linear with parameter β , then Error Φ has a contour of a ellipsoids. Maximum and minimum can then be found taking derivatives of the contour. However, when f is non-linear, contour will have irregular shapes.

Expanding y using Taylor series:

$$Y(Xi, b + \delta) = f(X_i, b) + \sum_{j=1}^{k} \left(\frac{\partial f_i}{\partial b_j} \right) (\delta_i)_j \tag{4.2}$$

β is replaced with b which is a converged least-square estimate of β. δ_i is the small correction to b. In equation 4.2, Y is linearly related to δ. Thus, by taking the derivative of the error in 4.1 with respect to δ, and setting the derivative to zero, an optimized β can be found.

4.2.2 Iteration to Get Least Error

In vector form, equation 4.2 can be written as

$$\Phi(b + \delta) = \sum_{j=1}^{k} \left(yi - f(x_i, \beta) - \left(\frac{\partial f_i}{\partial b_j} \right) (\delta_i)_j \right)^2 \tag{4.3}$$

where $\mathbf{J}$ is called Jacobian matrix whose (i,j) element is $\frac{\partial f_i}{\partial b_j}$. $\mathbf{J}$ is equivalent to a multidimensional concept of slope. When the slope is zero, the value of the function reaches the local minimum or maximum.

$$\mathbf{\Phi}(\beta + \delta) = |\mathbf{y} - \mathbf{f}(\beta) - \mathbf{J}\delta|^{\mathbf{2}} \tag{4.4}$$

Taking the derivative with respect to δ and setting the result to zero can lead to:

$$(\mathbf{J^T J})\delta = \mathbf{J^T}[\mathbf{y} - \mathbf{f}(\beta)] \tag{4.5}$$

Levenberg added a damping factor λ to provide a better approximation of the function $\mathbf{y}$.

$$(\mathbf{J^T J} + \lambda\mathbf{I})\delta = \mathbf{J^T}[\mathbf{y} - \mathbf{f}(\beta)] \tag{4.6}$$

where $\mathbf{I}$ represents the identity matrix. The factor λ adjusts the speed that error Φ is changing in each iteration. In particular, we would like to increase λ if we want Φ to decrease faster and decrease λ to make Φ decrease slower.

Later on, Marquardt modified equation 4.6 so that it allows us to step faster in the direction where the gradient is smaller and decrease step increments in the direction where the gradient is larger.

$$(\mathbf{J^T J} + \lambda\mathbf{diag}(\mathbf{J^T J}))\delta = \mathbf{J^T}[\mathbf{y} - \mathbf{f}(\beta)] \tag{4.7}$$

4.2.3 Best Fit Ellipse

The bioimpedance curve of measured tissue is fit with an ellipse using LM Algorithm. The fitted ellipse can be used to calculate parameters of electrical models in order to identify correlations with lymphedema. In this project, a program is written

to implement LM Algorithm in loops so that every iteration calculates λ to further optimize errors [6].

CHAPTER 5

IMPEDANCE DATA ANALYSIS

5.1 Delay Time

The signal received at detecting electrodes ideally should be a delayed version of the signal transmitted. The L-Dex machine sends a series of sinusoids from the electrodes at wrists sweeping through a range of frequencies. For each frequency, a corresponding signal with a delay should be detected. The delay time is a function of the path that the signal takes to go through the tissue, so it is consistent for all frequencies. L-Dex software does not present the delay time it uses to calculate the impedance, thus a program is written to derive the most probable delay time that the L-Dex system uses.

The raw data when plotted imaginary versus real part, show a hook shape. The curve shoots up at high frequency range. The curve traces from right to left as frequency increases from low to high as indicated by arrows in Fig. 5.1.

Applying an extra delay time to the impedance data alters the impedance curve. According to Cole model in previous sessions, the impedance curve should be a symmetrical ellipse form in general. A Matlab program is produced to find the best delay time that can result in a symmetric rounded curve.

The impedance is derived by the ratio of the transmitted voltage and detected current. A delay in time corresponds to a linear phase shift term.

$$Z_{corrected} = \frac{Z_{raw}}{e^{i2\pi t_d}} \tag{5.1}$$

After correction by phase shift, the high frequency shoot was decreased and bent down to form an elliptical pattern shown in Fig. 5.2.

After correction to the symmetrical rounded curve, the next step is to find the best fit ellipse and to abstract its geometric parameters.

5.2 Circle Fit

An ellipse lacks the uniform properties as in circles, so in order to fit an ellipse which has 4 parameters to fix: center of ellipse (x_0, y_0) and lengths of axes (R_x, R_y), fitting a circle is the first step.

The ellipse is tuned in a way that it is bisected by the point highest in imaginary versus real graph. Then, with the highest point on top of the circle, LM Algorithm helps find a best fit circle that provides the smallest mean square error in the vicinity of the highest top point in Fig. 5.2. LM Algorithm identifies the closest circle with the center (x_0, y_0) and radius (R_y).

5.3 Ellipse Fit

With parameters of the circle, expanding the radius in x direction while keeping the dimensions in y direction unchanged drags the circle to an ellipse.

As radius in x is incrementing, calculation of errors between data and ellipse acts as the indication of when the best fit ellipse is reached as shown in Fig. 5.4.

5.4 Cole Parameters

The Cole parameters are calculated from the geometric parameters of the impedance curve shown in Fig. 6.5. The details of calculating Cole parameters are explained in Chap.6

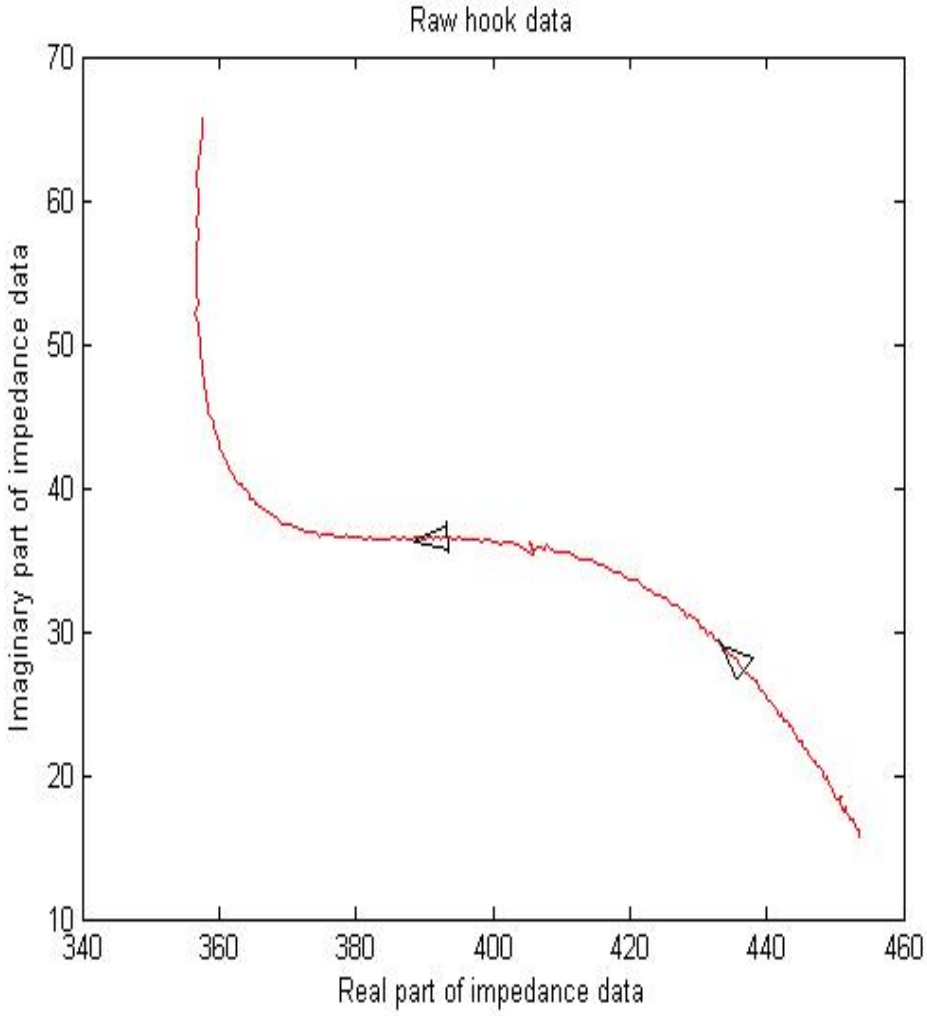


Figure 5.1: Impedance curve before Td correction

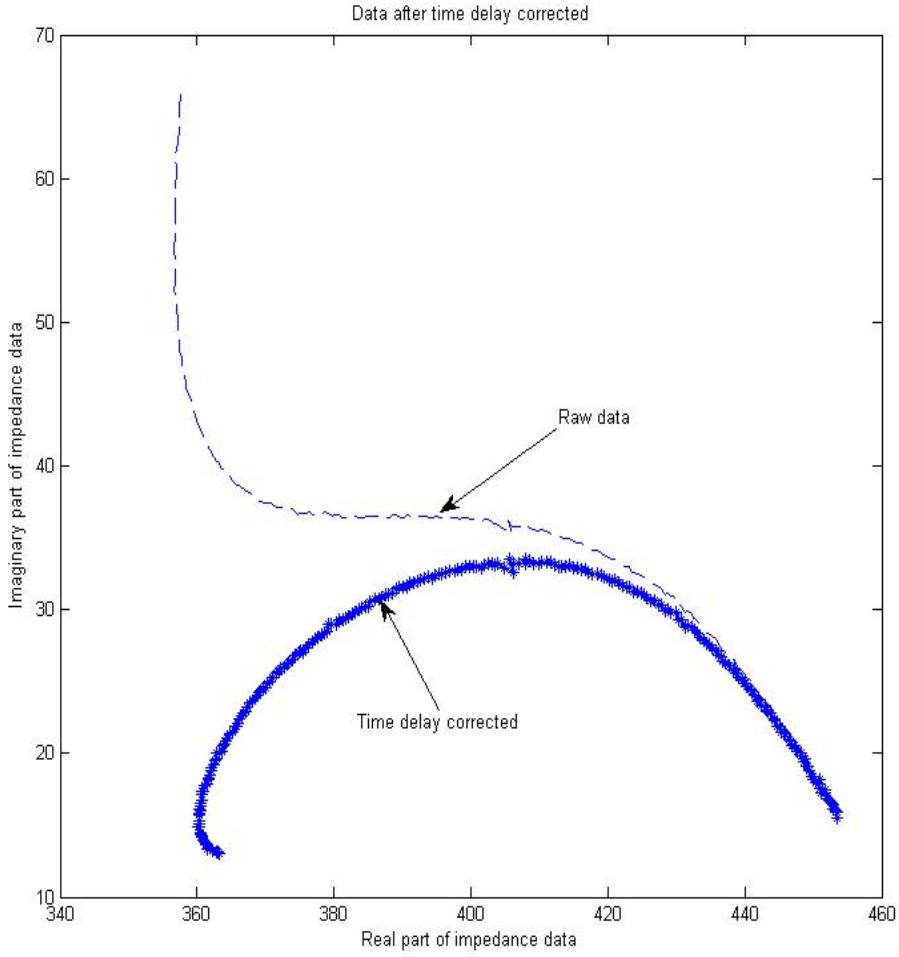


Figure 5.2: Impedance curve with Td correction

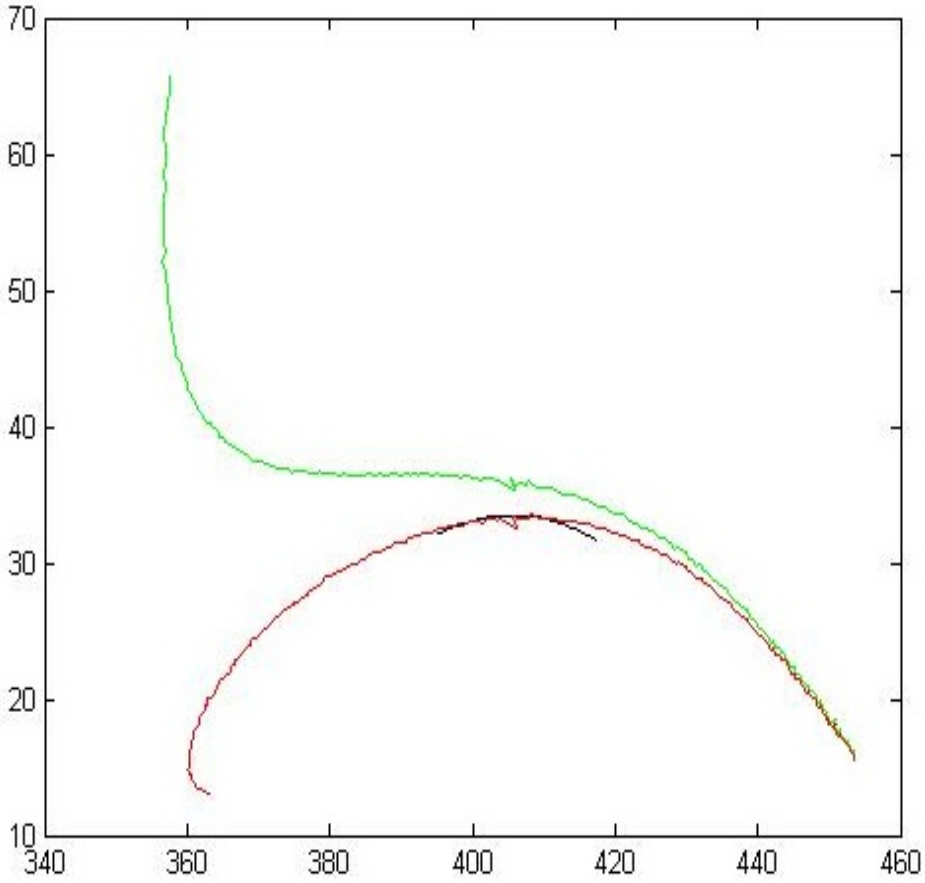


Figure 5.3: Best fit circle portion

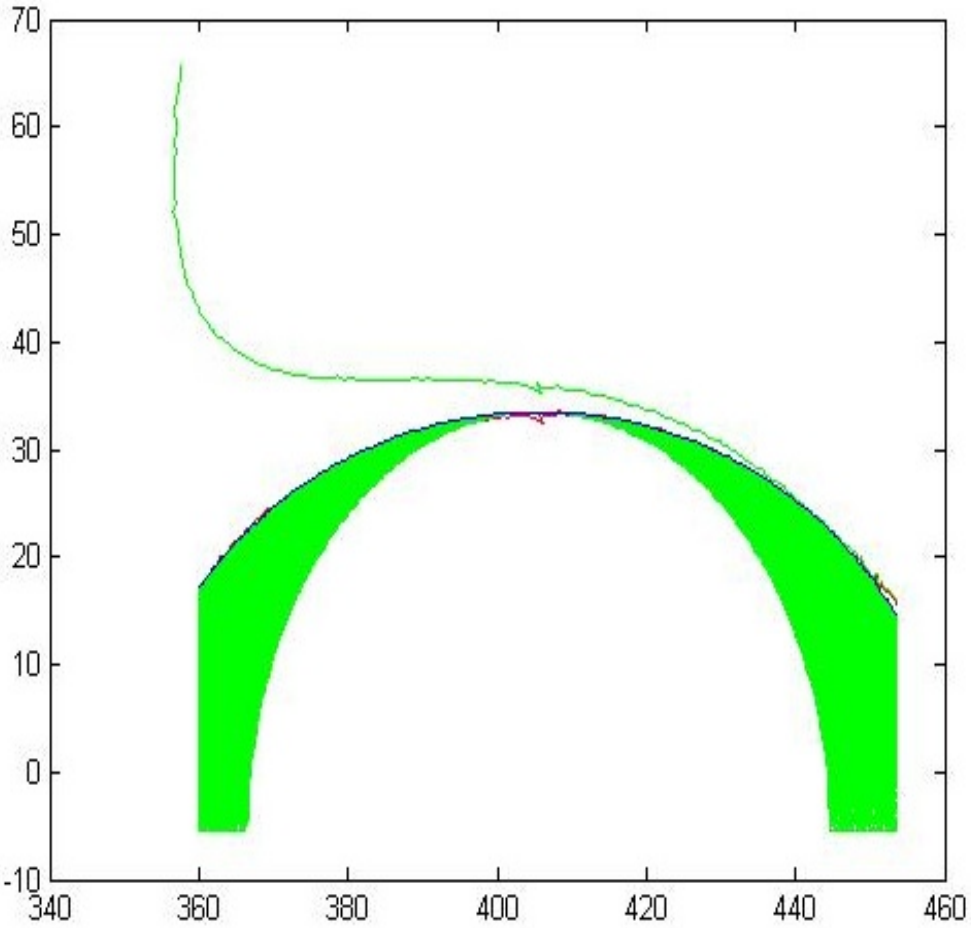


Figure 5.4: Best fit ellipse

CHAPTER 6

RESULTS AND DISCUSSION

6.1 Experiment Set Up

In this project, data are collected over 3 groups of subjects. One is the normal group which consists of healthy volunteers. The second is the confirmed lymphedema group. The last is an observation group which contains patients that are diagnosed with breast cancer and are going through multiple courses of treatment. The goal is to identify several parameters of the bioimpedance data that are correlated with development of lymphedema.

The detailed process of the project is listed below:

1. Test for repeatability of the bioimpedance machine.
2. Analyze bioimpedance data collected for all three groups.
3. Normalize affected side by the other side.
4. Compare lymphedema group with the normal volunteer group in order to identify the characteristics of the data that are correlated with lymphedema.
5. Simulate electrical circuit equivalents to model the body tissue.

6. Make changes to circuit model to account for changes in bioimpedance when patients develop lymphedema.

7. Apply identified criteria from step 4 on observation group to help diagnose lymphedema.

8. Follow the observation group over a period of time. Do regular measurements to track the conditions of the patients.

Lymphedema symptoms normally start to present gradually after surgery while the patients continue to be exposed to various surgeries and treatments. Following the conditions of the patients when they are going through the treatment can provide information of the effects of the treatments on causing lymphedema.

Unfortunately, to come up with a statistically significant conclusion, a large set of normal group and lymphedema group are required. Due to the limited time range of the project, we are not able to make statistically significant conclusions. There are many factors that can affect the bioimpedance information, such as the environment, dominant arms, the positions the electrodes are connected to patients and so on. This project also involves taking measurement on patients and using clinical data in research, so some unexpected time is spent applying for IRB approval and other permission of protocols. However, the lymphedema group seems to have distinguishable characteristics comparing to the other groups.

We only have 2 confirmed cases in Lymphedema group. Both of them suffer from long term lymphedema of late stages. Although 2 cases are far from enough to make generalized conclusions, both cases show different characteristics from the rest of subjects who are either healthy volunteers or breast cancer patients who have

Repeatability Test Results								
Patient	Side	Time	Geometeric parameters of impedance curve					
BI	L/R	Time lags	R_0	R_∞	Rx	Ry	x_0	y_0
BI19	Left	0	215.58	304.46	44.77	30.07	260.02	-3.66
BI19	Left	2 mins	223.35	302.92	39.78	26.08	263.13	-3.13
BI19	Left	5 mins	224.36	304.41	40.07	27.87	264.38	-3.45
BI19	Left	4 hours 54 mins	215.47	302.00	43.84	32.14	258.74	-5.22
BI19	Left	4 hours 57 mins	208.85	296.08	44.20	31.80	252.46	-5.19
BI20	Left	0	249.48	348.83	51.09	40.29	299.15	-9.44
BI20	Left	4 mins	255.42	344.02	44.73	35.03	299.72	-4.87
BI20	Left	8 days 2 hours	256.61	345.54	44.93	35.63	301.07	-5.12
BI20	Left	8 days 3 hours	258.91	347.08	44.68	35.58	303.00	-5.83

Table 6.1: Repeatability test results

not developed lymphedema yet. A more complicated Cole model can built to help explain the variation from normal.

6.2 Repeatability Test

The repeatability test evaluates the reliability of the equipment and data. The same technician takes measurements on the same patient several times in a day. Every few minutes or hours, a set of data is taken on the same patients. The repeatability test results are shown in Table 6.1.

Table 6.1 shows 6 geometric parameters of two patients. BI19 has 3 measurements 2 to 3 minutes apart, and then 2 measurements 5 hours later. The averages and percent errors are:

$$Average\ R_\infty = 217.5272;$$

$$RMS\ error R_\infty = 2.56$$

$$Error\ percentage R_\infty = 2.56/217.5272 = 1.17\%$$

Error percentage:

$$R_0 = 0.46\%$$

$$Rx = 2.26\%$$

$$Ry = 3.50\%$$

$$x_0 = 0.72\%$$

$$y_0 = 9.67\%$$

The same statistical analysis on error percentage is conducted on BI20:

$$R_\infty = 0.68\%$$

$$R_0 = 0.26\%$$

$$Rx = 2.95\%$$

$$Ry = 2.90\%$$

$$x_0 = 0.25\%$$

$$y_0 = 14.52\%$$

The calculated y_0 has the highest error percentage. But other parameters are very close. This proves the reliability of the measured bioimpedance data.

6.3 Electrical Equivalents Models of Body Tissue

We used a Cole model to characterize human limb tissue. The interpolated Wessel diagrams of bioimpedance to have two intersections with the real axis. One corresponds to the impedance of limb tissue at DC and the other corresponds to infinite frequency. The bioimpedance machine generates a signal with frequency ranges from

3kHz to 1MHz, so the data beyond the two frequencies are interpolated from the best fit curve mathematically. The two intersection with real axis are in fact intersections of the best fit curve with the real axis (R_0, R_∞).

For each patient, a Wessel diagram was plotted. Then as explained in detail in Chap.5, multiple data analysis actions finally led to a best fit ellipse. There are 4 geometric parameters that characterize an ellipse: coordinates of the center of ellipse (x_0, y_0), the major, Rx , and minor axis, Ry. Furthermore, the two intersections with real axis (R_0, R_∞) are also important. The patients are all deidentified and are assigned a label BI.

At DC frequency, impedance becomes purely real, which suggests a capacitor C1 in parallel with a resistor R1 (shown in Fig. 3.6). The impedance of the capacitor

$$Z = \frac{1}{jwC}$$

is infinity so the capacitor branch is open and the resistor dominates the impedance. $(R_0, 0)$ is the coordinate of the DC intersection.

$$R_0 = R1 \tag{6.1}$$

Following the same logic, when frequency goes to infinity, the capacitor is zero, so there has to be a resistor in series with the capacitor. The Cole model uses non linear capacitor and resistor in series so that the phase of the impedance on the capacitor branch is linear but the magnitude varies with frequency.

$$R_\infty = R1||R2 = \frac{R1R2}{R1 + R2} \tag{6.2}$$

The angle that the Wessel diagram forms with the real axis (Fig. 6.5) is directly related to α parameter in Cole model as in Eq. 3.17 and 3.18. The center frequency w_c is the frequency of the highest point on the curve. The capacitance C1 of the Cole model is derived:

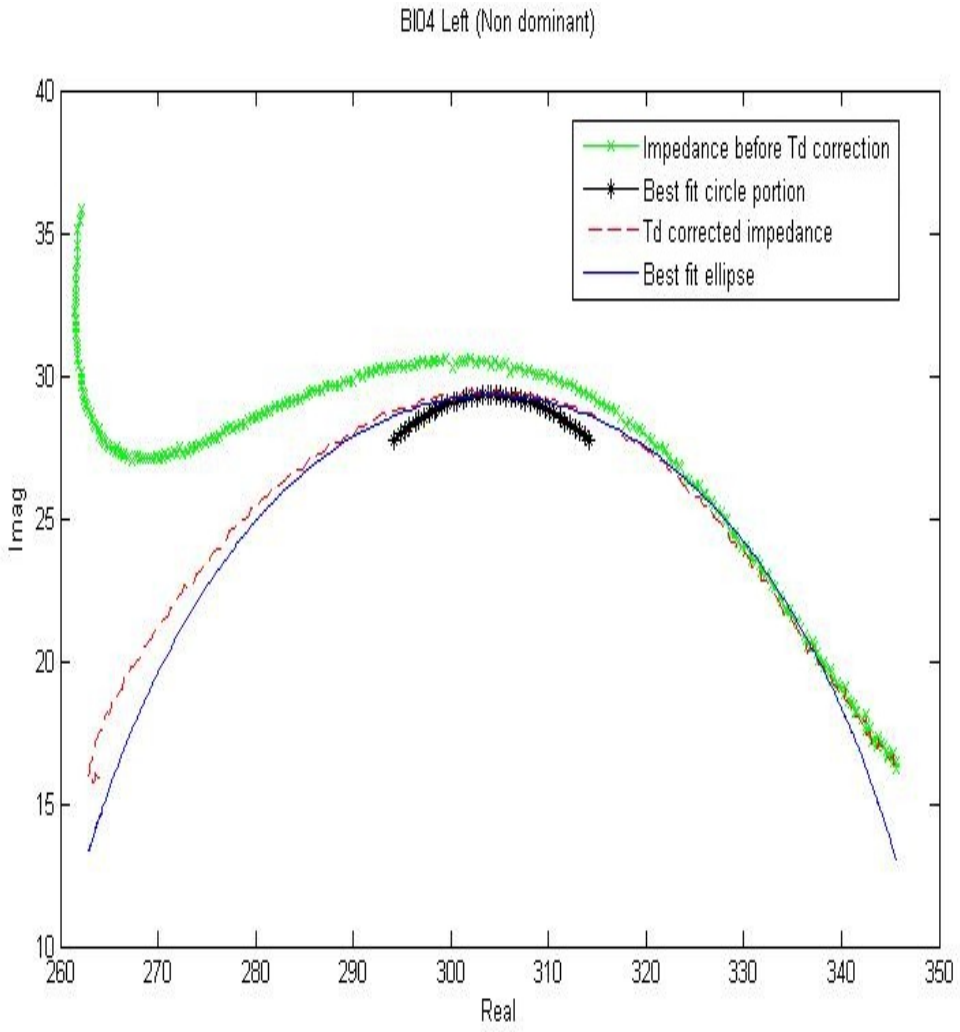


Figure 6.1: Long term lymphedema BI04 left side

$$w_c\tau = 1 \tag{6.3}$$

$$C1 = \frac{w^{\alpha-1}\tau^{\alpha}}{(R_{\infty} - R0)sin(\alpha\pi/2)} \tag{6.4}$$

6.4 Long Term Chronic Lymphedema

The two cases that are confirmed with lymphedema are label BI04 and BI18. Their bioimpedance curves are shown in Fig. 6.1, Fig. 6.2 and Fig. 6.3, Fig. 6.4. The bioimpedance curve reflects the amount of inter- and intra-cellular liquid and properties of membranes that are slightly different from person to person. So the impedance property of the affected limb is compared to the other side to eliminate the individuality of the bioimpedance. The best fit ellipses in the long term lymphedema cases are not well fit. The ellipse is higher than the impedance data at low frequencies and lower at high frequencies. Compare to Fig. 6.6 and 6.7, long term lymphedema curves are no longer symmetrical. Their highest point shifts to the left of the center line.

Fig. 6.9 and Fig. 6.10 show another perspective of long term lymphedema. Both figures have the patients' left and right sides together. Compare to a non-lymphedema patient BI11 in Fig. 6.11, the long term lymphedema shows larger deviation between the two sides of limbs. In a normal patient, the impedance curve only shifts horizontally, but the long term lymphedema patients' curves are different in shape as well. The affected side has taller and narrower curve.

In the two long term lymphedema cases, the Cole parameters are calculated from geometric parameters (listed in Table 6.2) using Eq. 6.1, 6.2, 6.4.

Patient	Side	Geometeric parameters of impedance curve					
BI	L/R	R_0	R_∞	Rx	Ry	x_0	y_0
BI04	Left	354.3811	256.9862	48.7055	30.0055	305.6836	-0.5462
BI04	Right	467.8464	343.8778	62.3592	45.6592	405.8621	-4.9992
BI18	Left	360.0272	256.3890	52.3833	33.0833	308.2081	-4.8422
BI18	Right	336.5391	247.7734	44.3841	24.5841	292.1562	-0.1822
BI11	Left	282.8032	203.4527	39.8944	29.4944	243.1279	-3.0869
BI11	Right	260.4688	185.5479	37.5895	27.9895	223.0083	-2.3169

Table 6.2: Long term lymphedema (BI04 and BI18) and normal (BI11) bioimpedance geometric parameters

Patient	Side	Cole parameters of impedance curve		
BI	L/R	R_0	R_∞	α
BI04	Left	354.3811	256.9862	0.513
BI04	Right	467.8464	343.8778	0.4423
BI18	Left	360.0272	256.3890	0.3949
BI18	Right	336.5391	247.7734	0.3800
BI11	Left	282.8032	203.4527	0.8743
BI11	Right	260.4688	185.5479	0.52

Table 6.3: Long term lymphedema (BI04 and BI18) and Normal (BI11) Bioimpedance Cole Parameters

The increasing imaginary impedance at high frequency indicates the loss of capacitance of the tissue. In long term lymphedema patients, the cell membranes are fibrotic. The semi-permeability of the membranes start to disappear. The membranes lose the ability to selectively absorb and export substances. Instead, all molecules such as ions, water, proteins pass through the membranes with little resistance. This is reflected in the decrease of capacitance.

Cole parameters are subsequently calculated from the geometric curve in Table 6.3.

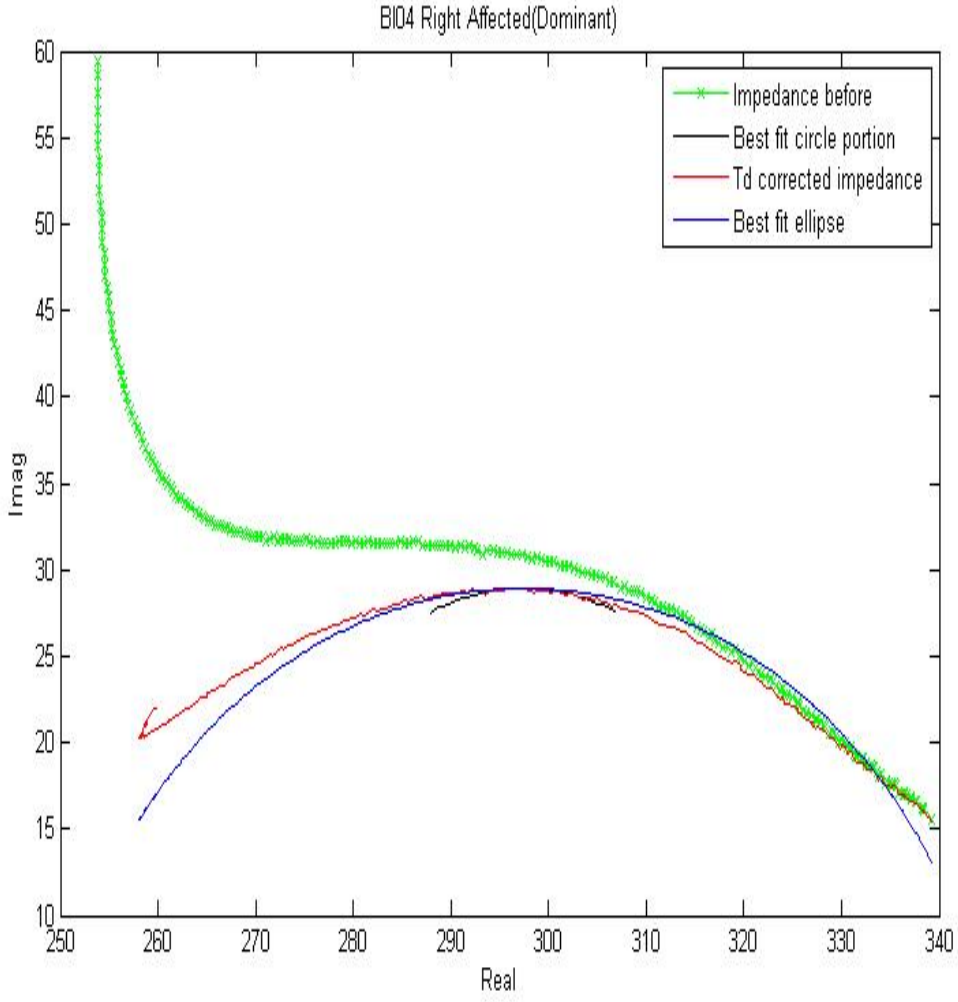


Figure 6.2: Long term lymphedema BI04 right side

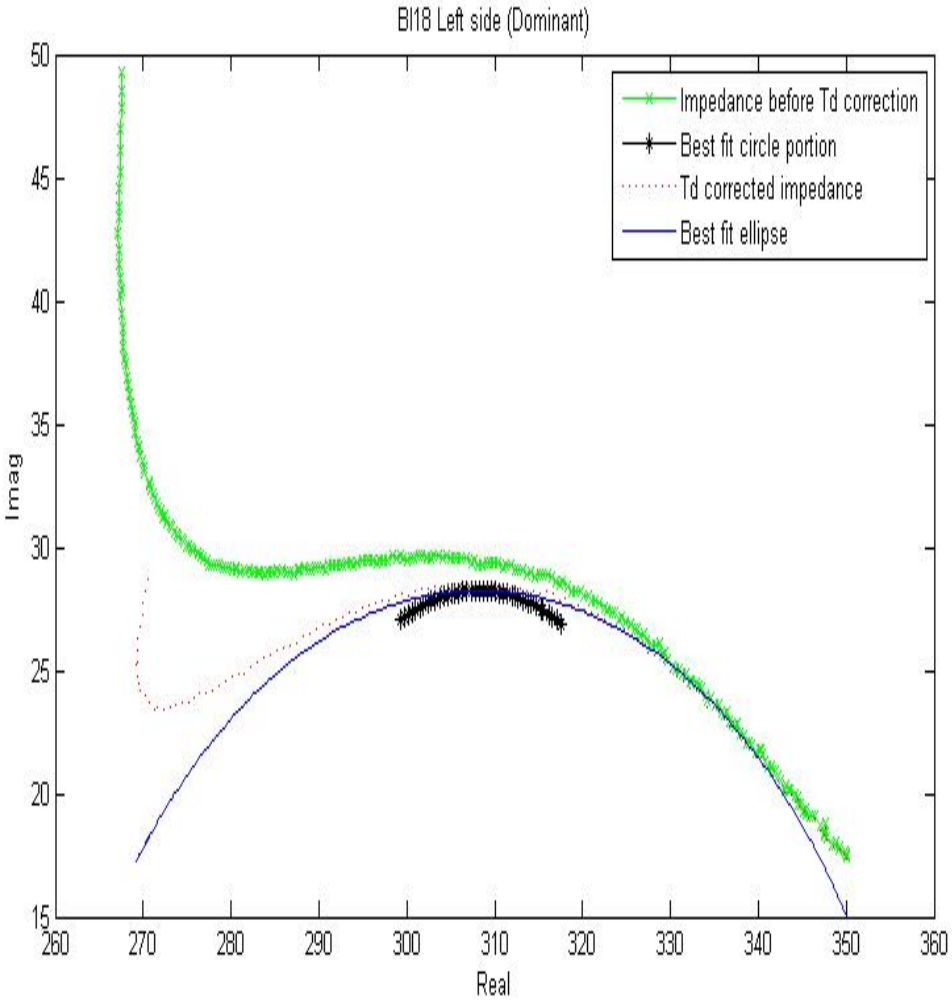


Figure 6.3: Long term lymphedema BI18 left side

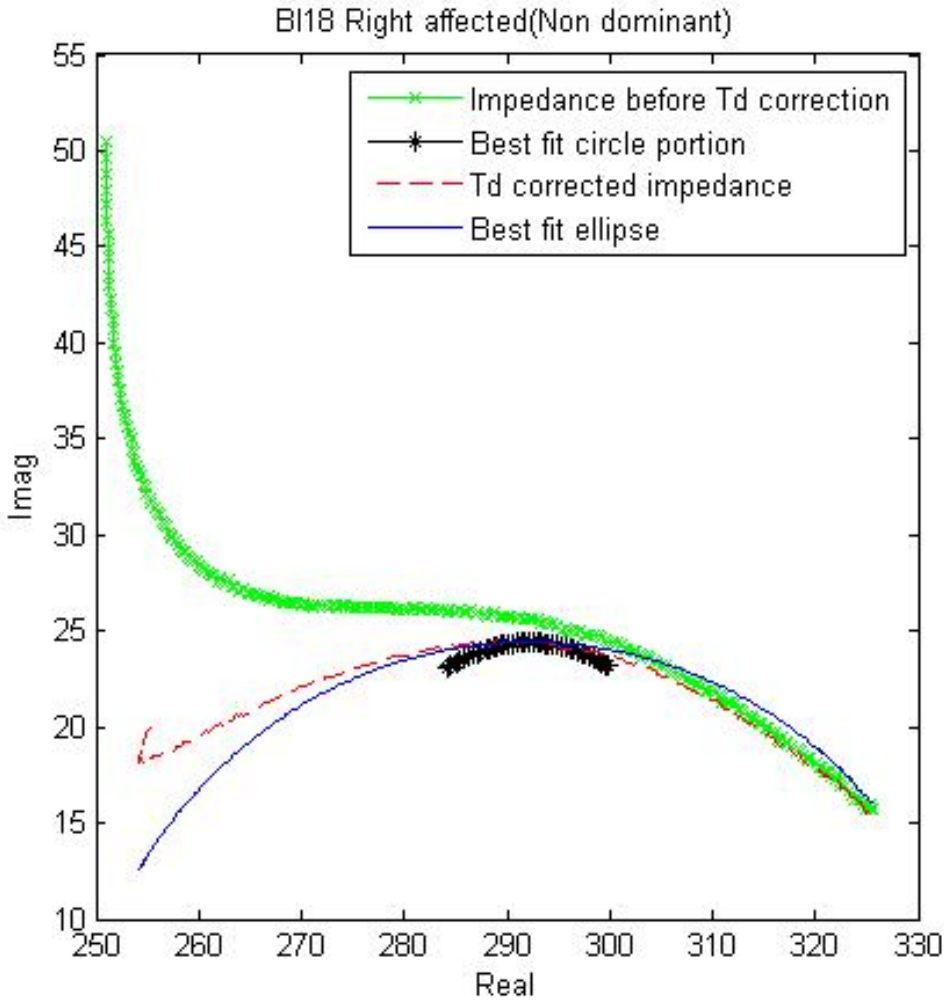


Figure 6.4: Long term lymphedema BI18 right side

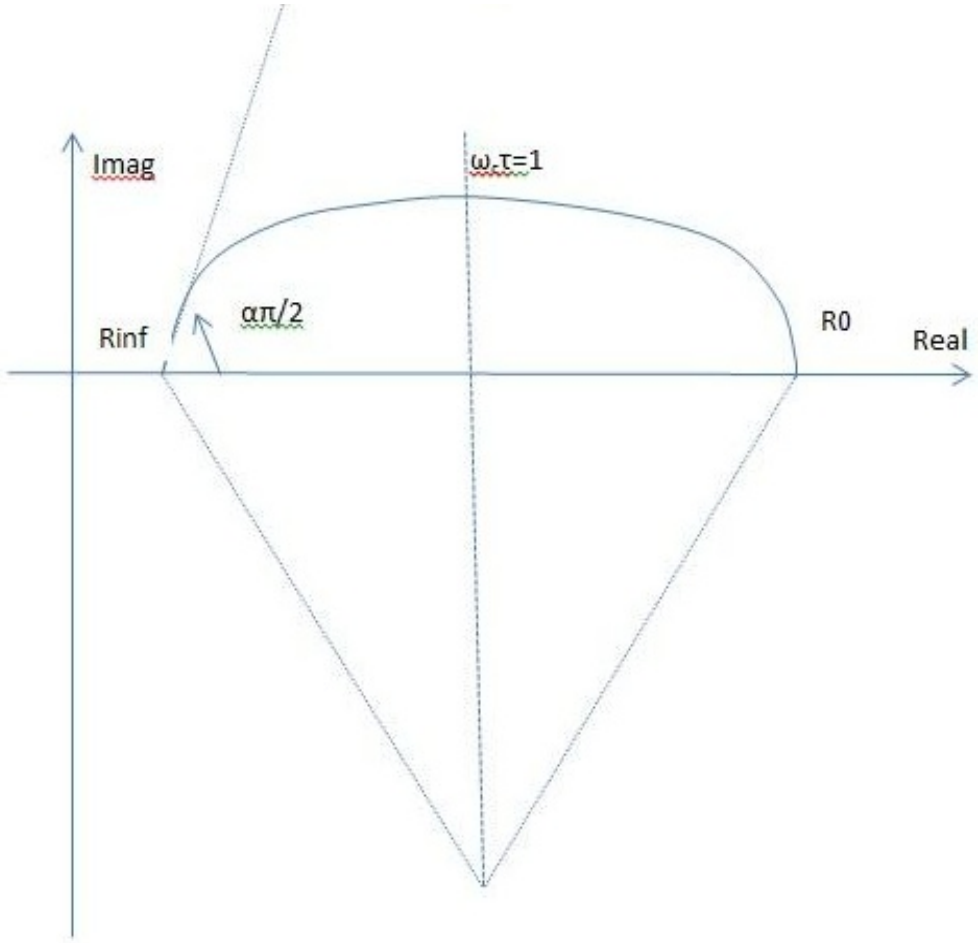


Figure 6.5: Cole Y model Wessel diagram- relation between geometric parameters and Cole model parameters

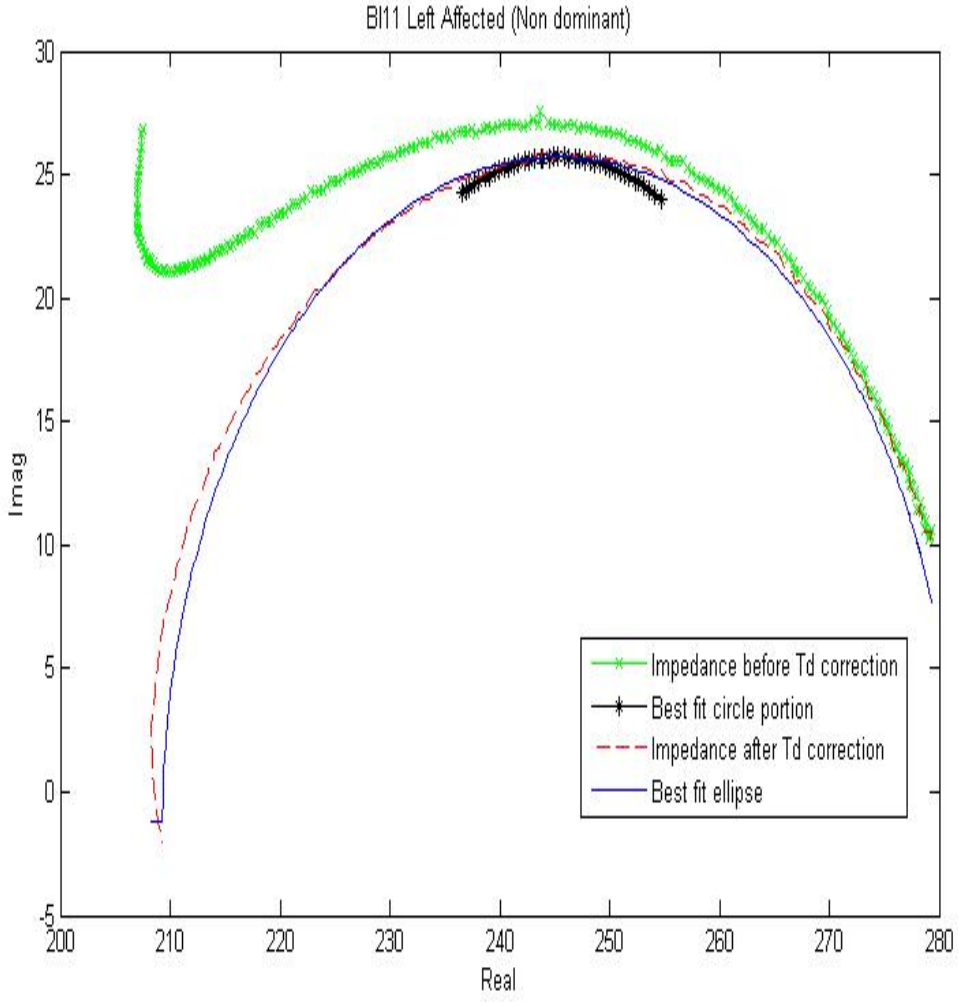


Figure 6.6: Normal BI11 left side

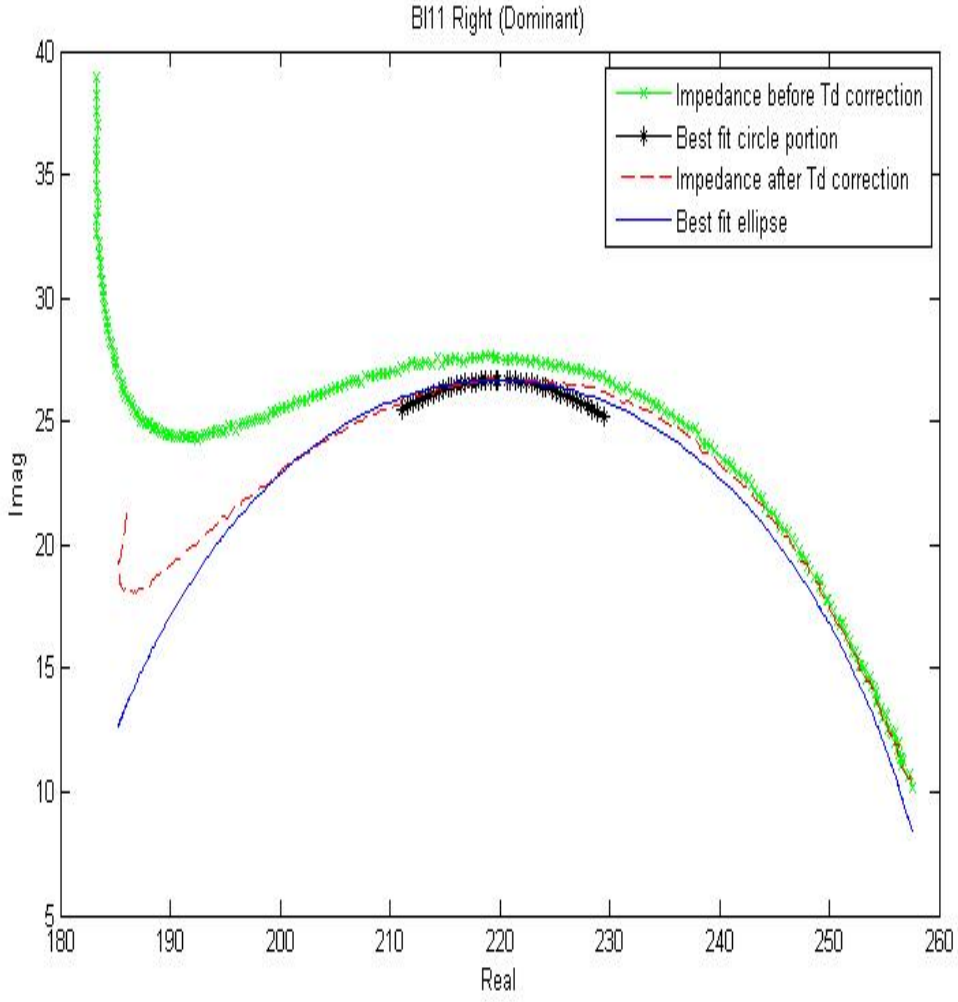


Figure 6.7: Normal BI11 right side

Figure 6.8: BI04 Best Fit Ellipse

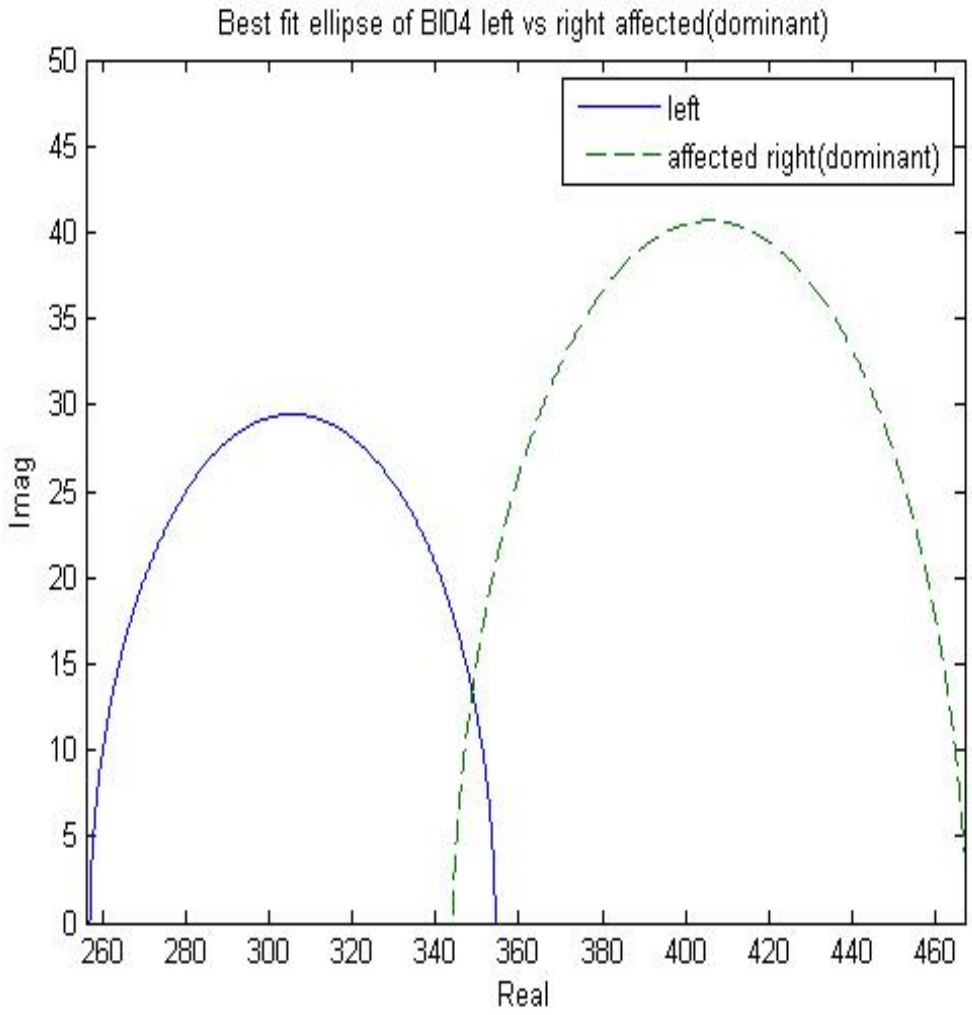


Figure 6.9: BI04 best fit ellipse

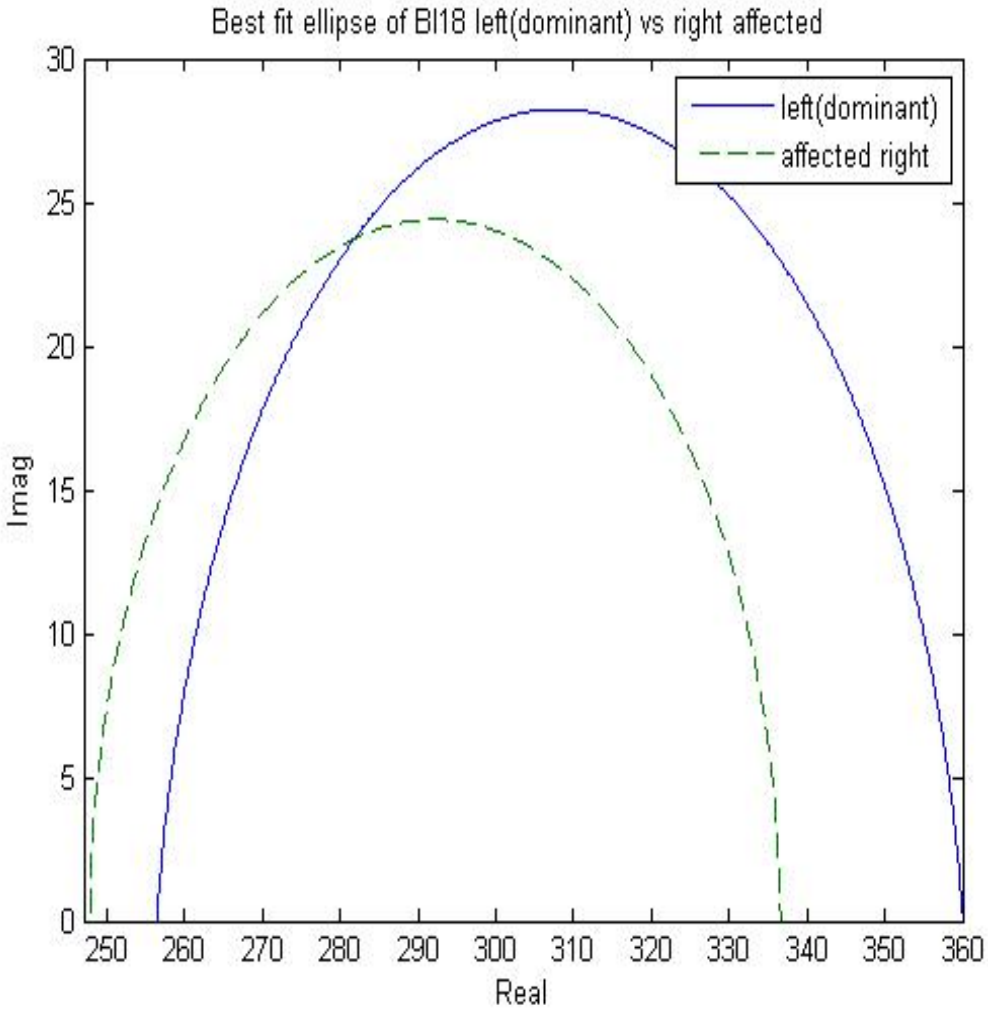


Figure 6.10: BI18 best fit ellipse

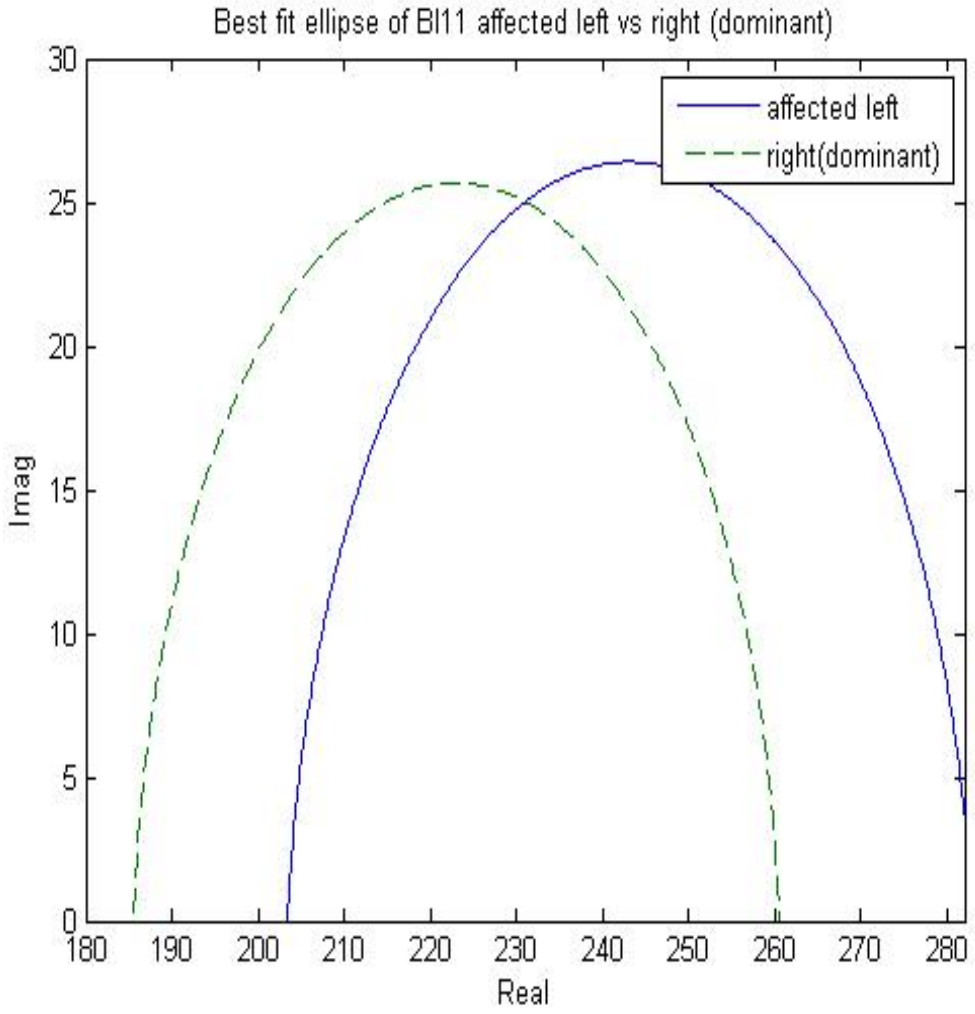


Figure 6.11: BI11 best fit ellipse

CHAPTER 7

DEVIATION FROM COLE MODEL

7.1 Tear Drop

The impedance curve we analyzed shows a slightly different pattern than the typical Cole model, especially for the patients with confirmed long term lymphedema. In the Cole model, the impedance Wessel curve is circular or elliptical in general but the data of lymphedema patients presents a tear drop shape. The highest point on the curve is not in the center so the curve is not symmetric any more as shown in Fig. 6.4. Cole Model only allows the phase of the impedance to vary with frequency, so the curve is still elliptical. In reality, more degrees of freedom might be required. The high frequency region has a larger imaginary part than the low frequency area. Delay time correction changes the shape of the impedance curve, but within the range of nano-seconds delay time which is the time signal travels approximately the height of the person, the corrected shape is tear drop like with higher imaginary part at MHz area.

Cole model has been a popular electrical model for healthy tissue, but in long-term lymphedema cases, the model does not represent the swelling tissue very well.

7.2 Influence Factors

There are many influence factors that can cause the bioimpedance curve to deviate from the normal. For safety reasons, the signals the bioimpedance generate have to be low in voltage magnitude. But this creates potential chances for errors. The detectors of the bioimpedance machine are also designed to be sensitive to small magnitude signals. Crosstalk signals that are comparative in magnitude are all noise that could affect the interpretation of the data.

7.2.1 Environment

All measurements were taken in James Cancer Center of the Ohio State University. The test room where all measurements are taken was originally only separated by a thin wall from the electrical room of the building. As a result, all noise signals from electrical devices are collected by the bioimpedance machine. The repeatability test originally showed data of large error percentage. In January 2011, the James Center breast cancer division moved to a new location and so the data collected have a better reliability. The errors in repeatability test are acceptable in the new location.

7.2.2 Dominant Arm

Most people use their dominant arms more than the other side. The dominant side is usually physically stronger. The side that lymph nodes are removed from in surgery will be vulnerable to complications such as lymphedema. The bioimpedance characteristics of a patient whose affected arm is the dominant arm would be different from a patient whose affected arm is the non-dominant arm. In our study, both

lymphedema cases have their right arms affected but BI04's dominant arm is the right while BI18 is the left.

7.2.3 Positions of Electrodes

In order to have common reference points, the position the electrodes are connected on the patients have to be easy to access and repeat. Different technician or even the same technician at various times of the day can hook the electrodes at slightly different places on the patients. In this project, all data are measured by electrodes at patients' wrists and ankles. Small variations in positions still exist and might vary the results of the impedance.

7.2.4 Swellings

Patients just out of surgery will generally swell a little, which is the natural reaction to injuries. But this swelling tends to disappear given some time for the patient to recover. The swelling due to lymphedema will exacerbate and eventually degenerate to fibrotics.

CHAPTER 8

CONCLUSION AND CONTRIBUTION

8.1 Conclusion

Due to the insufficient amount of data available and the limited time the project could last, the conclusions are not statistically significant. Among the three groups of subjects in the experiment, the observation group has not been observed for long enough to diagnose any patients with lymphedema. However, important parameters are identified to show strong correlations with lymphedema. The two cases with long term lymphedema do not fit the Cole Model which has been widely used to simulate healthy tissue. Confirmed lymphedema patients have observed bioimpedance Wessel curve that is closer to a tear drop shape. The span and height of the bioimpedance Wessel diagram all present significant deviation from the normal side of the same patient. Further research on more complicated models is required to characterize lymphedema tissue. Looking at more subjects may show statistical significance of that deviation from the Cole model and perhaps non-Cole parameters could be determined to better explain and stage the disease.

8.2 Contribution

This project studied the bioimpedance properties of long term lymphedema patients. A Cole Model does not provide a good simulation for fibrotic lymphedema tissue. More complicated models are possible subjects for future studies.Perhaps relaxing CPE approach and decoupling real and imaginary parts of impedance or admittance could better suit a lymphedema tissue electrical model. Bioimpedance is relatively sensitive to small signals, so it could potentially show signs of lymphedema before the symptoms start to present. It is much faster and cheaper than MRI and other imaging method to study soft tissue. It is still a valuable direction for future research.

8.3 Multiple Element Models

Multiple resistors and CPEs can be included in the model to account for non-symmetries and variation. Cole Models with a larger number of elements may better model the body tissue. Fig. 8.1 shows several possible circuits equivalents that have purely real impedance at 0 and ∞ frequencies.

Fig. 8.2 shows the corresponding Wessel characteristic of the multiple element models in Fig.8.1, where Wessel diagrams were generated using freq range 3kHz to 1MHz as is available in the Bioimpedance machine.

8.3.1 More Degrees of Nonlinearity

Cole model uses CPE to allow the magnitude of the element to vary with frequency on an order of α. The phase is independent of frequency. Fibrotic lymphedema tissue may require a more general phase in terms of frequency.

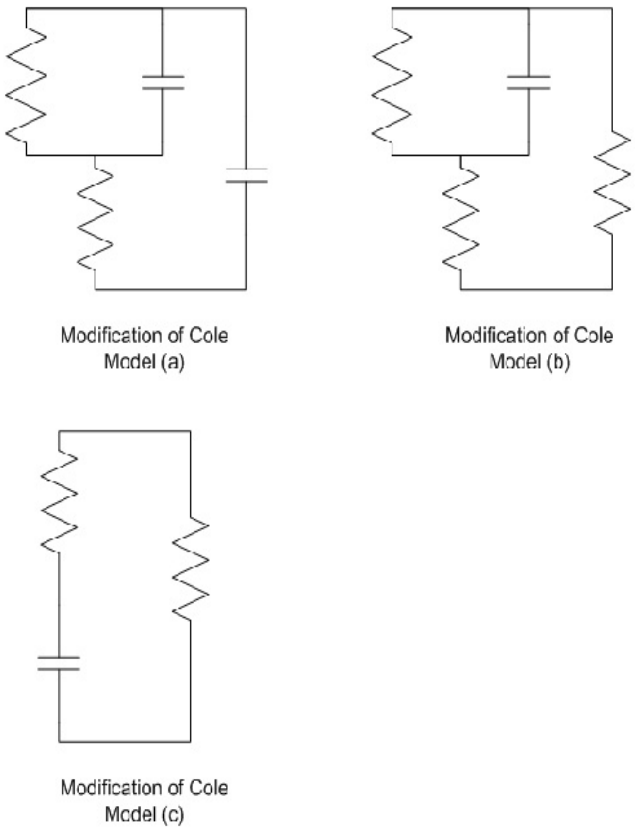


Figure 8.1: Add extra elements to Cole model to account for the deviation

8.3.2 Limit the Scope of Tissue Measured

L-Dex machine used in this project can only measure the bioimpedance characteristic of the entire body from wrist to ankle. The electrodes are attached to the surface of the skin. The methods are prone to errors and many influence factors. A biopsy of the swelling tissue can be a better object to take measurement. So the bioimpedance results are limited solely on the affected tissue.

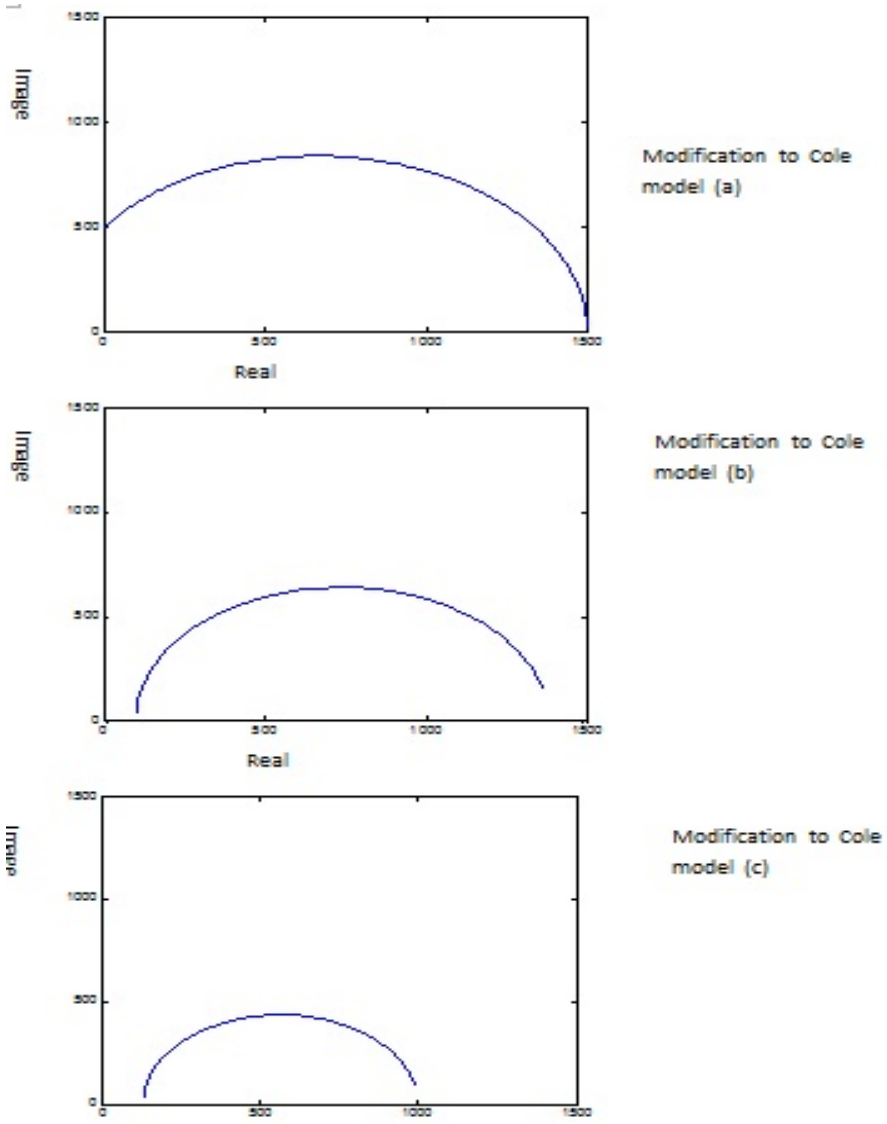


Figure 8.2: Wessel diagram of the modification of Cole model

APPENDIX A

MATLAB CODE

```
clear

clc

clf

%  filename='data.xlsx';

% [S,string]=xlsread(filename,9);

%S=BI03_1;

%% Change ID

%BI01,BI02,BI03_1,BI03_2,BI04,BI05,BI06,BI11

load('Halfdata.mat','BI14');

S=BI14;


%% Change Arm

% _(257:512) Left Arm_ (1:256) Right Arm


 Td=1.000*10^-8;
```

```
 F=S(257:512,2)+i*S(257:512,3);
 plot(S(257:512,2),S(257:512,3),'g');
 %legend('raw hook data');
 hold on
 %% Change error range
 Tderr=0.0300;
 Tdrange=8.50*10^-8;
 Fiterr=0.30;
 shift=4;
 %%




   while Td<Tdrange
  for k=1:1:length(S(1:256,1))
G(k)=F(k)*exp(-i*2*pi*S(k,1)*1000*Td);
  end
 x=real(G);
 y=imag(G);
 %plot (x,y,'r');
 yright=y(2:200);
[a,b]=max(yright);
omiga=S(b,1)*2*pi;
q=1:1:95;
```

```
 for k=1:1:length(q)
slope_r(k)=abs((y(b+q(k))-y(b))/(x(b+q(k))-x(b)));
slope_l(k)=abs((y(b-q(k))-y(b))/(x(b-q(k))-x(b)));
diff(k)=abs(slope_r(k)-slope_l(k));
 end
% y_1d=zeros(1,59);
% y_2d=zeros(1,59);
% curvature=zeros(1,59);

% for m=10:1:55
% y_1d(m)=(y(m+1)-y(m))/(x(m+1)-x(m));
% end
% for n=10:1:54
% y_2d(n)=(y_1d(n+1)-y_1d(n))/(x(n+1)-x(n));
% curvature(n)=y_2d(n)/(abs(1+y_1d(n).^2).^1.5);
%
% end

% num=abs(Radius_est^2-(x-x0_est).^2);
% curvature=(-4*sqrt(num)-(x-x0_est).^2./sqrt(num))./(4.*num);
%err=sqrt(mean((curvature-mean(curvature)).^2));
err=sqrt(mean((diff-mean(diff)).^2))
 %if (max(curvature)-min(curvature))>0.4
 if err>Tderr
```

```
     Td=Td+10^-10;
     disp('Td no match');
     %plot (x,y,'r')
 else disp('Td found');
     %save('GeoPara','GeoPara(1,2)')
       plot (x,y,'r')
  %legend('time delayed data');
  hold on
     break;

 end
  end
%   figure(2);
% plot([59:-1:1],curvature);




% for k=1:1:length(q)
% slope_l(k)=(y(b)-y(b-q(k)))/(x(b)-x(b-q(k)));
% slope_r(k)=(y(b+q(k))-y(b))/(x(b+q(k))-x(b));
% end


%%
 %yright=y(1:50);
```

```
 %[a,b]=max(yright);
 [a,b]=max(y);
 b=b+shift;
% c=find(x>*x(1));
% [a,b]=max(y(c));%take mean if b if vector
%c=find(y>=0.85*a);
%k=round(mean(c));
%x0i=x(k);
x0i=x(b);
%yp=(y(b-2)+y(b-1)+a+y(b+1)+y(b+2))/5;
yp=y(b);
%y1=(y(1)+(2)+y(3)+y(4)+y(5))/5;
y1=y(1);
%x1=(y(1)+(2)+y(3)+y(4)+y(5))/5;
x1=x(1);
xt=x((b-20):(b+20));
yt=y(100:140);
l=sqrt((x1-x0i)^2+(yp-y1)^2);
thita=asin(yp/l);
Radiusi=l/2/sin(thita);
y0i=-(Radiusi-yp);
n_iters=120; % set # of iterations for the LM
lamda=10^(-3); % set an initial value of the damping factor for the LM
updateJ=1;
```

```
x0_est=x0i;

y0_est=y0i;

Radius_est=Radiusi;

yi=sqrt(-(xt-x0i).^2+Radiusi^2)+y0i;

%Gi=(x-x0i).^2+(y-y0i).^2;

plot(xt,yi,'b')

hold on

for it=1:n_iters

if updateJ==1

% Evaluate the Jacobian matrix at the current parameters (x0_est, y0_est)

J=zeros(239,3);

%syms x0 y0 Radius

for j=1:1:41

% J(i,:)=jacobian((sqrt(-(x(i)-x0)^2+Radius^2)+y0),[x0,y0,Radius]);

% x0=x0_est;

% y0=y0_est;

% Radius=Radius-est;

J(j,:)=[-(x0_est-xt(j))/sqrt((-(xt(j)-x0_est)^2+Radius_est^2)),

1,Radius_est/sqrt(-(xt(j)-x0_est)^2+Radius_est^2)];

end

% Evaluate the distance error at the current parameters

y_est = sqrt(-(xt-x0_est).^2+Radius_est.^2)+y0_est;

d=yt-y_est;

% compute the approximated Hessian matrix, J is the transpose of J
```

```
H=J'*J;
%if it==1 % the first iteration : compute the total error
e=dot(d,d);  %(d*d)
end
%end
% Apply the damping factor to the Hessian matrix
H_lm=H+(lamda*eye(3,3));
% Compute the updated parameters
J_cut=J(1:41,:);
d_cut=d(1,1:41);
dp=-inv(H_lm)*(J_cut'*d_cut');
x0_lm=x0_est+dp(1);
y0_lm=y0_est+dp(2);
Radius_lm=Radius_est+dp(3);
% Evaluate the total distance error at the updated parameters
y_est_lm = sqrt(-(xt-x0_lm).^2+Radius_lm.^2)+y0_lm;
d_lm=yt-y_est_lm;
e_lm=dot(d_lm,d_lm);
% If the total distance error of the updated parameters is less
%than the previous one
% then makes the updated parameters to be the current parameters
% and decreases the value of the damping factor
if e_lm<e
lamda=lamda/4;
```

```
x0_est=x0_lm;

y0_est=y0_lm

Radius_est=Radius_lm;

e=e_lm;

disp(e);

updateJ=1;

elseif (e_lm-e)<=0.0001

    updateJ=0;

    lamda=lamda/2;

else % otherwise increases the value of the damping factor

updateJ=0;

lamda=lamda*5;

%disp(it);

end


end

plot(xt,y_est,'k');




%%

plot (x,y,'r');

hold on
```

```
Rx=Radius_est;
%Rx=30
while Rx<95

    y_plot=y0_est+sqrt(Radius_est^2-Radius_est^2./Rx^2.*(x-x0_est).^2);
    figure (1)
    %plot(x(1:256),y_plot(1:256),'g');
    hold on
    %for n=1:1:length(y_plot)
        %difference=abs(y-y_plot);

        error_diff=sqrt(mean((abs(y(1:220)-y_plot(1:220))-
mean(abs(y(90:110)-y_plot(90:110)))).^2));
        %figure (2)
        %plot (error_diff,'*')
        %hold on

          if error_diff<Fiterr

            disp('Rx fit')
            %plot(x,y_plot,'b')
            %title('BI05_left')
            break;
        else Rx=Rx+0.1;
```

```
            %disp('Rx not fit')
          end



end
r_inf=-Rx*sqrt(1-y0_est^2/Radius_est^2)+x0_lm
r_0=Rx*sqrt(1-y0_est^2/Radius_est^2)+x0_lm
eval(['Rx=','Rx'])
eval(['Ry=','Radius_est'])
eval(['x0=','x0_est'])
eval(['y0=','y0_est'])



%%
load structure_data;
%  BI=struct('Index',{'LeftRight','LeftRight','LeftRight','LeftRight',
%'LeftRight','LeftRight','LeftRight'}, ...
%            'x0',{188.8114 272.8467 293.6301  },  ...
%            'y0',{ -1.3553 -7.3938 -9.5229 },  ...
%            'ID',{'BI01','BI02','BI03_pre',}, ...
%            'Rx',{33.6715   46.1605   },   ...
%            'Ry',{24.6715   34.5605   },    ...
%            'Td',{1.0e-007 *0.1740  }, ...
%            'r_0',{222.4321  317.9385  },  ...
```

```
%            'r_inf',{155.1908  227.7550  } )
%% Change ID and Arm
% *Change Arm*
%  k=1 Left  k=2 Right
IDnum=18;
k=1;



BI(IDnum).x0(k)=x0;
BI(IDnum).y0(k)=y0;
BI(IDnum).Rx(k)=Rx;
BI(IDnum).Ry(k)=Ry;
BI(IDnum).Td(k)=Td;
BI(IDnum).r_0(k)=r_0;
BI(IDnum).r_inf(k)=r_inf;
BI(IDnum).ID='BI14';


%%
save('structure_data','BI');
```

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